ORIGINAL CLINICAL RESEARCH

Efficacy and Safety of Pyridostigmine Addition to the Conventional Treatment of Postdural Puncture Headache: A Randomized Controlled Clinical Trial

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Abstract

Background: Most management approaches of postdural puncture headache (PDPH) remain uncertain due to lack of evidence of benefit. This study aimed to assess the useful effects as well as safety of pyridostigmine as an added therapy for pain control in obstetric patients with severe PDPH following spinal anesthesia.

Methods: This randomized, double-blind, clinical trial recruited women aged 20-40 years who underwent elective cesarean delivery under intrathecal anesthesia and diagnosed with a severe PDPH with a visual analog scale (VAS) score of five or greater. Thirty eligible patients were randomly allocated into two groups. Patients in the pyridostigmine group received 60 mg oral pyridostigmine every six hours, while those in the placebo group received placebo tablets every six hours. Both groups received conventional care. Outcomes were recorded and analyzed.

Results: At six hours, the VAS score was significantly lower in the pyridostigmine group than in the placebo group (2.0 vs. 7.0, $p<0.001$). At 24 hours, the VAS score was 0.0 in the pyridostigmine group versus 5.0 in the placebo group, and this effect persisted through 72 hours. The epidural blood patch was not required patients who administered pyridostigmine. Alternatively, two patients required the patch in the placebo group ($p=0.483$). The most frequent side effects in the pyridostigmine and placebo groups were nausea and vomiting (26.7% vs. 33.3%), neck stiffness (20.0% vs. 13.3%), abdominal cramps (13.3% vs. 6.7%), and muscle spasms (6.7% vs. 0.0%), with no significant differences (all $p=1$).

Conclusion: Adding pyridostigmine to conventional care was effective in managing pain intensity and reducing its duration in obstetric patients with PDPH.

Keywords: Elective Cesarean Section; Pain Score; Postdural Puncture Headache; Pyridostigmine; Spinal Anesthesia.

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Introduction

Postdural puncture headache (PDPH) is commonly reported following neuraxial anesthesia. PDPH is more common after epidural anesthesia and is related to the accidental puncture of the dura during the attempted placement of a catheter in the epidural space.[1] Alternatively, the use of smaller needles for spinal anesthesia makes PDPH incidence less frequent after spinal than with epidural anesthesia.[2]

The incidence of PDPH varies widely, depending on the patient and the procedure. Young age, female sex, low body mass index, pregnancy, and vaginal delivery increase the risk of PDPH.[3] Obstetric women have many risks for developing PDPH including their gender, and young age, besides the prevalent use of neuraxial blocks.[4, 5]

Patients with PDPH typically have positional headaches which are frontal or occipital which becomes worse with sitting or standing, and are relieved by lying flat. Severe headaches are accompanied by nausea, vomiting, neck stiffness, low back pain, tinnitus, vertigo, and vision changes such as diplopia, blurred vision, or photophobia.[6]

PDPH usually resolves spontaneously, though there is an increased risk of longer-term or persistent headaches in some cases.

In obstetric patients, PDPH is an unpleasant experience and can be incapacitating. It might restrict the capability of the mother to take care of herself or her baby, increase the duration of her stay in the hospital, or progress into a chronic headache.[5,7] Therefore, prompt diagnosis and treatment are essential.

The initial management of PDPH is conservative measures that include complete bed rest, intravenous fluids administration, caffeine and analgesic supplementation. If pain continues with no response to the conservative treatment within two days, more aggressive interventions are indicated. In the case of moderate and severe headaches, an epidural blood patch is considered a definitive treatment. However, this invasive technique has inherent risks for some complications such as back pain, spinal subdural hematoma, infection, or subdural abscess.[8]

Some drugs have been investigated for the treatment of PDPH such as neostigmine/atropine, gabapentin,

hydrocortisone, theophylline, and sumatriptan. But there is still limited evidence of their benefits.[9, 10]

Pyridostigmine is an acetylcholinesterase inhibitor that is used to decrease muscle weakness resulting from myasthenia gravis.[11] Scremin et al.[12] documented that central pyridostigmine in the CSF could modulate the tone of cerebral blood vessels through augminting the acetylcholine effects.

This study aimed to evaluate the useful effects as well as safety of pyridostigmine as an added therapy in the treatment of severe PDPH following spinal anesthesia in obstetric patients.

Materials And Methods

Ethical considerations

The study was carried out following agreement of the Ethics Committee of the Faculty of Medicine Suez University (19-2-2023). We obtained a written informed consent from each patient, and we maintained confidentiality of the data by making a code number for each patient. We registered this study at ClinicalTrials.gov (ID: NCT05969119).

Study design, settings and date

This clinical trial was randomized, controlled, double-blinded, and parallel-group with a 1:1 allocation ratio that was undertaken at Suez General Hospital, Suez, Egypt between July 2023 and January 2024.

Sample size

We used power analysis and sample size software (PASS), version 15.0.10 for sample size calculation. At power of 80%, a significance level of 0.05, and an effect size based on a difference in the median VAS after 72 hours between patients with postdural puncture headache (PDPH) who took neostigmine with conventional management (Median: 1, IQR: 0-2) and those who took saline with conventional management (Median: 5, IQR: 4-6), and after considering 20% dropout rate, the minimum required sample size was 30 patients (15 patients in each group).

Eligibility criteria

We included participant who underwent elective cesarean delivery under anesthesia through the intrathecal spinal space and complained of headache related to the puncture of the dura. Other inclusion criteria included the age group from 20 to 40

years, and an American Society of Anesthesiology physical status of II. We adopted the International Headache Society criteria for diagnosing the PDPH.[13]

We excluded patients with a visual analog scale (VAS) score <5, a history of chronic headache, cluster headache, migraine, seizures, cerebrovascular accident, previous neurological disease, signs of pre-eclampsia or eclampsia, coagulopathy, and severe bleeding (>20% of blood volume), as well as patients treated with vasopressors and those with bronchial asthma, arrhythmia, or any type of heart block.

Randomization

Computer-generated random numbers and sealed opaque envelopes were used for randomization and allocation concealment.

Blinding

This clinical trial was blinded both for the participants assignment and the researcher who evaluated the participants after the procedure. Both were unaware of the assignment. In addition, the medications were prepared by an anesthesiologist not involved in the trial.

Procedures and interventions

Eligible patients with postoperative PDPH and VAS score ≥5 were randomized into two groups (15 patients each). Patients in the pyridostigmine group received 60 mg oral pyridostigmine every six hours. In the placebo group, patients received placebo tablets (similar in shape to pyridostigmine tablets) every six hours.

We continued the intervention until achieving a VAS score of three or lower, or for 72 h. Patients in the pyridostigmine group who achieved a VAS score ≤3 before 72 h were continued on an oral placebo every 6 hours to maintain blinding.

To ensure the recommendations of the World Health Organization, we instructed the participants to refrain from breastfeeding all over the 24 hours following the last dose of pyridostigmine and to use a breast pump to relieve breast engorgement.

Both groups received conventional management consisting of rest in the supine position, IV fluids in the form of 30 mL/kg/day Ringer's lactate, and administration of 1 g paracetamol plus 135 mg caffeine every 6 hours. Following the approved protocol for controlling the postoperative pain at our institution, Ketoprofen at a dosage of 100 mg in the form

of suppositories were recommended two times per day for five days.

In both groups, intrathecal spinal anesthesia was accomplished by an anesthesiologist who was not involved in the study. First, intravenous fluid preloading with 10 mL/kg Ringer's lactate was done. Then, intrathecal blocks were performed in the sitting position with 2.5 mL of hyperbaric 0.5% bupivacaine (12.5 mg) at L3-L4 using a 22-gauge spinal needle.

Data collection and study outcomes

Participants' baseline data, including age, weight, and height, as well as the delay time between dural puncture and the start of headache were recorded. The main outcome was a 10-cm VAS assessment of headache severity at 0, 6, 12, 24, 36, 48, and 72 hours following the procedure after requesting the patient to sit upright for 15 minutes. Additional outcomes included the need for an epidural blood patch and any adverse effects, including the development of nausea and vomiting, neck stiffness, abdominal cramps, muscle spasms, bronchospasm, and urinary bladder hyperactivity. The epidural blood patch was indicated based on either a VAS of five or more at 72 hours after the patient's consent or the patient’s request at any time.

Statistical Analysis

All data were tabulated and analyzed using the statistical package for the social sciences, IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA). Qualitative data were presented with numbers and percentages and compared using Fisher's exact test. Numerical data were tested for normality using the Shapiro-Wilk test. Data that followed a normal distribution d were described as mean and standard deviation and compared using the independent T-test, while skewed data were presented as median and interquartile range (25th-75th percentiles) and compared using the Mann-Whitney U test. We adopted a cutoff p-value of less than 0.05 for statistical significance.

Results

A total of 33 patients were assessed for inclusion in the study. Two patients were excluded for migraine headaches. Additionally, one patient declined to participate. The 30 eligible subjects randomly allocated to receive either pyridostigmine or a placebo (15 participants each). All patients in both groups completed follow-up and were involved in the final statistical analysis (Figure 1).

The mean ages of patients in the pyridostigmine and placebo groups were comparable, with no significant difference (27.7±5.9 and 30.3±6.3, respectively, p=0.255). The body mass index was significantly higher in the placebo (30.2±2.9) than in the pyridostigmine (28.0±2.1) groups, (p=0.023). The onset of PDPH was 9.5±5.2 h in the pyridostigmine group and 9.9±4.5h in the placebo group, with no significant difference (p=0.852) (Table 1).

The baseline median VAS scores before the interventions were not significantly different (medians: 8.0 vs. 7.0, p=0.512). At six h after intervention, the median VAS score was significantly lower in the pyridostigmine group than in the placebo group (2.0 vs. 7.0, respectively, p<0.001). A similar result was observed at 12 h with a median VAS of 1.0 in the pyridostigmine group and 5.0 in the placebo group. The pyridostigmine was highly effective in relieving headache at 24 h following its administration, with a median VAS of 0.0 compared to 5.0 in the placebo group, and this effect continued throughout the study period till the 72 h time point. A significant large treatment effect (effect size r) was observed at all time points from six to 72 h (Table 2).

At 6h after the intervention, the incidence of achieving a VAS score ≤3 showed a significantly higher frequency in the pyridostigmine (86.7%) than in the placebo group (13.3%), (p<0.001). As of 12 h following the intervention, all (100%) patients in the pyridostigmine group had a VAS score of ≤3 compared to 20.0% at 12 h, 13.3% at 24h, 20.0% at 36h, 26.7% at 48 and 72 h in the placebo group (Table 3).

None of the pyridostigmine group participants required the epidural blood patch, but 2 out of the 15 control patients required the blood patch (p=0.483). The recorded adverse effects in the pyridostigmine and placebo groups were nausea and vomiting (26.7% vs. 33.3%), neck stiffness (20.0% vs. 13.3%), abdominal cramps (13.3% vs. 6.7%), and muscle cramps (6.7% vs. 0.0%), with no significant differences (All p-values=1). No patients in either group developed bronchospasm or urinary bladder hyperactivity (Table 4).

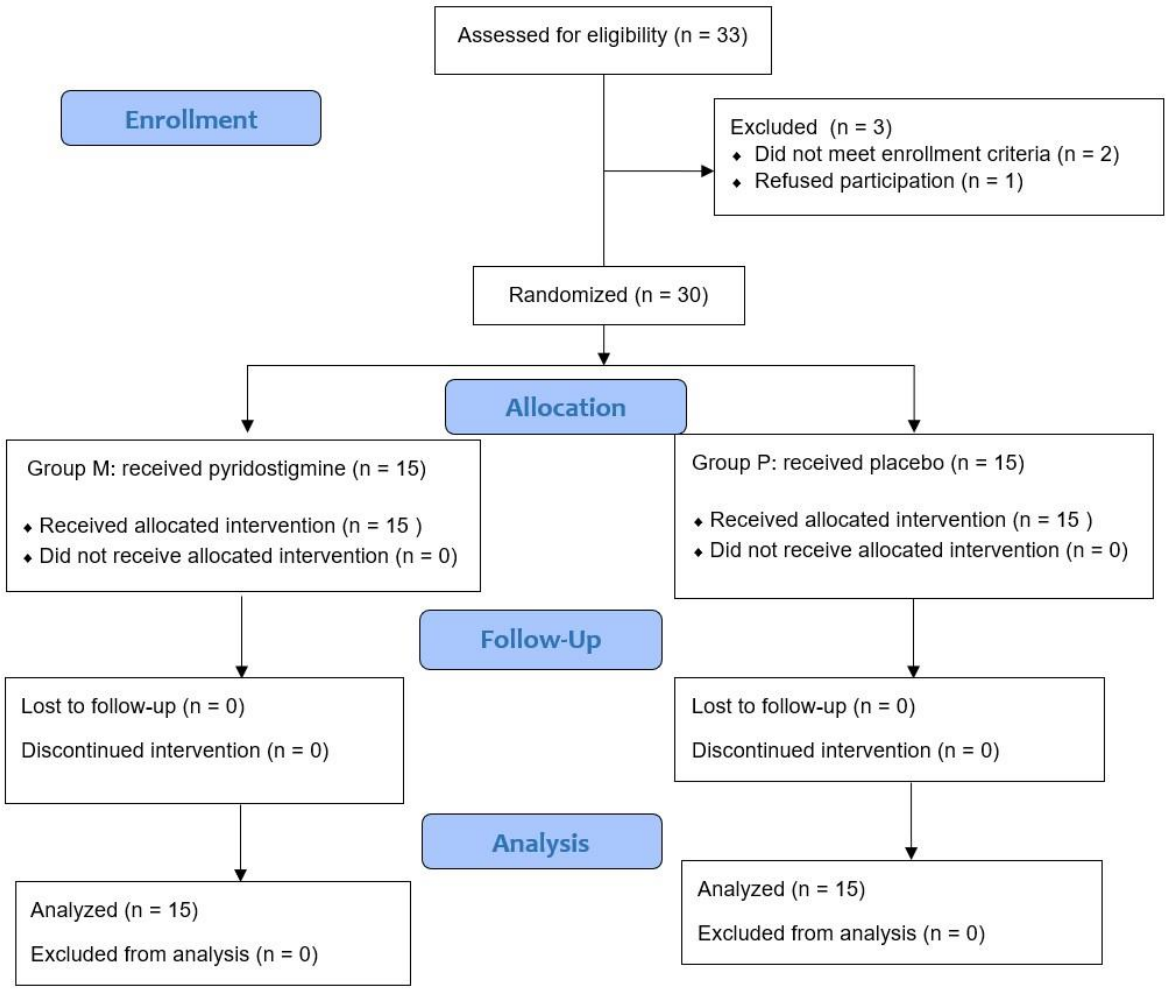

Figure 1. The trial flow diagram.

Table 1. Basic data of the studied pyridostigmine and placebo groups.

	Pyridostigmine Group (n=15)	**Placebo Group (n=15)**	**P-value**
Age, year	27.7±5.9	30.3±6.3	0.255
BMI, kg/m^2	28.0±2.1	30.2±2.9	0.023*
Onset of PDPH, h	9.5±5.2	9.9±4.5	0.852

Data is presented as mean ± standard deviation.
n: number, SD: standard deviation, BMI: body mass index, PDPH: postdural puncture headache.
*Significant at $p<0.05$

Table 2. Assessment of VAS scores recorded

VAS scores	Pyridostigmine Group (n=15)	Placebo Group (n=15)	P-value	Effect size r	Effect size Interpretation
Before intervention	[7-8]	[6-7]	0.512	NA	NA
				NA	NA
6h after the intervention	[1-2]	[4-8]	<0.001*	0.776	Large effect
12h after the intervention	[0-1]	[4-6]	<0.001*	0.836	Large effect
24h after the intervention	[0-1]	[4-6]	<0.001*	0.852	Large effect
36h after the intervention	[0-1]	[4-6]	<0.001*	0.852	Large effect
48h after the intervention	[0-1]	[3-6]	<0.001*	0.738	Large effect
72h after the intervention	[0-1]	[3-6]	<0.001*	0.545	Large effect

Data is presented as Median and IQR.
NA: not applicable; VAS: visual analog scale
*Significant at $p<0.05$

Table 3. Incidence of achieving a VAS score ≤3.

VAS score ≤3	Pyridostigmine Group (n=15)	Placebo Group (n=15)	P-value
6 h after the intervention	13 (86.7%)	2 (13.3%)	<0.001*
12 h after the intervention	15 (100%)	3 (20%)	<0.001*
24 h after the intervention	15 (100%)	2 (13.3%)	<0.001*
36 h after the intervention	15 (100%)	3 (20%)	<0.001*
48 h after the intervention	15 (100%)	4 (26.7%)	<0.001*
72 h after the intervention	15 (100%)	4 (26.7%)	<0.001*

Data is presented as number (percentages)

VAS: visual analog scale

*Significant at $p<0.05$

Table 4. Incidence of Epidural blood patch requirement and treatment-associated side effects.

	Pyridostigmine Group (n=15)	**Placebo Group (n=15)**	**P-value**
Requirement of Epidural blood patch	0 (0%)	2 (13.3%)	0.483
Nausea and Vomiting	4 (26.7%)	5 (33.3%)	1.00
Neck stiffness	3 (20%)	2 (13.3%)	1.00
Abdominal cramps	2 (13.3%)	1 (6.7%)	1.00
Muscle cramps	1 (6.7%)	0 (0%)	1.00
Bronchospasm	0 (0%)	0 (0%)	NA
Urinary bladder hyperactivity	0 (0%)	0 (0%)	NA

Data is presented as number (percentages)

NA: not applicable

Discussion

Despite the known benefits of spinal anesthesia, PDPH remains a challenging complication of this technique. The management of PDPH is heterogeneous in many institutions because of the absence of clear guidelines and protocols. According to the recent clinical practice guidelines for PDPH, most management approaches remain uncertain due to the paucity of evidence, and there is a need for future research to improve the quality of care.[14] Hence, we aimed to explore the effectiveness and safety of using the cholinergic drug, pyridostigmine, for pain control in obstetric patients having severe PDPH following spinal anesthesia.

It has been reported that the gauge of the spinal needles significantly affects the incidence and the severity of PDPH. The thicker the needle, the higher the incidence of severe headaches following spinal anesthesia.[15] Unfortunately, the available spinal needle for elective cesarean delivery at our institution was a 22-gauge size because it is cost-effective.

The results of this study indicate the usefulness of pyridostigmine in decreasing the duration and intensity of severe PDPH. The oral administration of pyridostigmine significantly lowered pain scores compared to the conservative treatment starting from six h following the intervention. A greater difference in pain scores was documented at 12 h; patients in the pyridostigmine group showed a median VAS much lower than the control group. The highest pain-relieving effect of pyridostigmine was observed at 24 h and this large significant effect continued till 72 h following the intervention.

Furthermore, the magnitude of pyridostigmine efficacy was large, and this was observed in the high success rate of oral pyridostigmine in relieving pain and inducing a VAS score of three or less compared to the placebo treatment. Hence, pyridostigmine use was associated with enhanced recovery. Additionally, none of the patients who received pyridostigmine members requested the epidural blood patch compared to two patients in the placebo group.

Several previous studies reported similar findings to those in the current study for managemnet of PDPH. A recent RCT concluded that neostigmine intake by nebulization at a dose of 20 µ/kg in addition to atropine at a dose of 10 µ/kg diluted in 4 mL normal saline was associated with rapid relief of PDPH after cesarean section, with a significant decrease in VAS score compared to the control group (median VAS: 2 vs. 5).[16] In another RCT, patients having severe

PDPH who rated a VAS score of five or more following elective cesarean section under spinal anesthesia were allocated either to neostigmine at a dose of 20 μg/kg administered by slow IV injection and atropine at a dose of 10 μg/kg diluted in 20 mL of normal saline given over five minutes every eight hours or 20 mL of normal saline IV every eight hours. There was a significant decrease in VAS scores at 6, 12, 24, 36, 48, and 72 time points following the intervention. The IV neostigmine/atropine achieved a VAS score ≤ three after two doses (16 h).[17] The use of pyridostigmine in our study has the advantage of oral administration. Pyridostigmine is similar to neostigmine, but it has the advantages of higher oral bioavailability and, a longer duration of action than neostigmine, besides a milder adverse effect profile.[18]

The exact cause of headache occurrence after puncture of dura is uncertain. However, it is assumed to be related to a leak of cerebrospinal fluid (CSF) through the created hole in the dura mater by the needle resulting in CSF hypotension. The low CSF pressure can lead to compensatory meningeal vasodilation and blood volume expansion or stretching of sensory intracranial nerves.[19]

Cerebral blood flow is regulated by vasomotor, chemical, metabolic, and neurogenic mechanisms.[20] Pyridostigmine is an orally active reversible inhibitor of cholinesterase enzyme that hydrolyzes acetylcholine in the synaptic cleft.[11] The quaternary ammonium compounds can't penetrate the blood-brain barrier but they can penetrate the blood-CSF barrier.[21, 22] The inhibition of acetylcholinesterase by pyridostigmine increases the acetylcholine levels in the CSF and subsequently in the brain. Acetylcholine causes initial direct depolarization of the ganglia in the cerebrospinal tissues resulting in constriction of cerebral vessels.[23] Thereby, Pyridostigmine can counteract the proposed cerebral vasodilation mechanism of the PDPH.

Adverse reactions of pyridostigmine may be muscarinic or nicotinic, and both types are related to the increased acetylcholine neurotransmitter. Muscarinic reactions include nausea, vomiting, diarrhea, abdominal cramps, increased salivation, bronchospasm and increased bronchial secretions, and urinary urgency. The main nicotinic effects are muscle cramps and fasciculations.[24]

In the current study, monitoring of the patients for self-reported adverse effects

revealed non-significant differences between the pyridostigmine and placebo treatments regarding the incidence rates of nausea and vomiting (26.7% vs. 33.3%), neck stiffness (20.0% vs. 13.3%), abdominal cramps (13.3% vs. 6.7%), and muscle cramps (6.7% vs. 0.0%). No patients in either group developed bronchospasm or urinary bladder hyperactivity. Moreover, the recorded side effects were well tolerated by the patients, and none stopped the treatment due to the drug-related side effects or required medical intervention.

This randomized clinical trial evaluated an inexpensive and readily available therapeutic intervention for the management of a common disabling complication following spinal anesthesia in obstetric patients. Bias was minimized by masking the group assignment both for the participants and the researcher who collected data, and by being placebo-controlled. However, it is limited by its single-center design. Future mechanistic studies that include measurement of cerebral blood flow and CSF pressure and monitoring of plasma and CSF kinetics of pyridostigmine are needed.

Conclusions

The results indicate that oral pyridostigmine was effective in the treatment of severe PDPH following spinal anesthesia for elective cesarean section. The use of pyridostigmine significantly reduced pain scores and headache duration and did not require additional use of the epidural blood patch. It was also safe and well tolerated.

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Conflict of interest:

The authors declare no competing interests.

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